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[see original article on page 619](#)

# Renal ischemia–reperfusion injury: Renal dendritic cells loudly sound the alarm

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**Renal ischemia–reperfusion injury is a major cause of acute renal failure and kidney allograft dysfunction. Dong and colleagues now identify the surveying renal dendritic cell network as the predominant source of tumor necrosis factor- $\alpha$  during the early stages of renal ischemia–reperfusion injury, raising the possibility for direct targeting of renal dendritic cells to help ameliorate this common form of renal injury and its sequelae.**

*Kidney International* (2007) **71**, 604–605. doi:10.1038/sj.ki.5002121

Against the physician's credo “do no harm,” renal ischemia–reperfusion injury (IRI) stands as an anathema. As if the clinical burden from renal IRI secondary to other causes isn't enough, kidney transplant care teams everywhere face daily the irony that at some point, the patient's remedy, a kidney allograft, must first suffer an unavoidable and troublesome insult: complete ischemia during transfer from the donor to the recipient, followed by reperfusion once vascular anastomosis in the recipient is complete. To counter the jeopardy this poses to

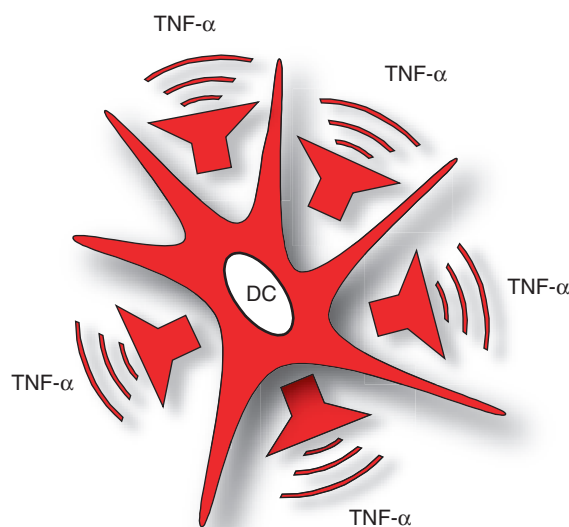
kidney function in the recipient, investigators have worked diligently for years in clinical settings and in the laboratory to understand the pathophysiology of renal IRI and to devise ways to lessen its detriment to the allograft. Notwithstanding the great strides resulting from these efforts, renal IRI continues to factor into delayed graft function, acute rejection, and chronic allograft nephropathy.

Along the cascade of pathogenic events that cause renal IRI, there has been an appreciation for the early innate immune response within the kidney itself and its role in priming the kidney for further injury. One puzzling question, however, has been which populations of cells resident within the kidney are most important in mediating this ‘sterile’ inflammatory response. Thanks to a study by Dong and colleagues<sup>1</sup> (this issue), some answers

are now provided. Dong *et al.* proceed in their research on renal IRI under the precept that the immediate innate immune responses to parenchymal injury anywhere within the kidney are orchestrated by resident immune cells, specifically renal dendritic cells (DCs), that are designed to survey for and respond to cellular damage.<sup>1</sup> This immunologic paradigm was recently buttressed by the discovery of the contiguous renal DC network in normal kidney.<sup>2</sup> By carefully fractionating resident renal DCs from other immune and nonimmune renal cells after inducing renal IRI, and by selectively ablating resident renal DCs with clodronate liposomes before inducing renal IRI, Dong *et al.*<sup>1</sup> demonstrate that resident renal DCs are the predominant source of intrarenal tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in early renal IRI (Figure 1).

Although other cytokines and chemokines produced by resident renal DCs probably play a role in the pathogenesis of renal IRI, the seemingly limited focus by Dong *et al.* on TNF- $\alpha$ <sup>1</sup> is well founded. Soluble TNF- $\alpha$  can be abundantly expressed by mononuclear phagocyte lineages (for example, myeloid DCs and macrophages), natural killer cells, and certain T-lymphocyte effectors (for example, T-helper 17 (Th17) and Th1 lymphocytes) and mediates its effects by engaging TNF receptor-1 (TNFR-1), which is normally present at basal levels on most quiescent cells, and TNFR-2, which is normally present on endothelial cells and some leukocytes.<sup>3</sup> This pleiotropic reservoir of TNF- $\alpha$ -responsive cell types explains TNF- $\alpha$ 's harmful effects when its synthesis and release are poorly controlled.<sup>3</sup> During renal IRI in the allograft, for example, the substantial early production of TNF- $\alpha$  by resident renal DCs<sup>1</sup> and the subsequent activation of adjacent TNFRs could induce apoptosis of renal epithelium,<sup>3</sup> and, thus, the generation of alloantigen, all the while causing upregulation of adhesion molecules on renal endothelium, thereby promoting extravasation of the recipient's leukocytes into the allograft. Among several possibilities, the latter could include preexisting populations of T-lymphocyte effectors that further propagate renal IRI<sup>4</sup> or the recipient's own trafficking DCs, ready to

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**Figure 1 | Renal DCs sound the alarm in renal IRI.** TNF- $\alpha$  is abundantly expressed by renal DCs but not by other renal cells in early renal IRI.

scavenge and present alloantigen. Indeed, increased levels of intrarenal TNF- $\alpha$  in early renal IRI have already been shown to strongly predict adverse outcomes for kidney allografts.<sup>5</sup>

The predominant production of TNF- $\alpha$  by resident renal DCs over other renal cells in early renal IRI<sup>1</sup> invokes the conundrum of how lipopolysaccharide (LPS) injures the kidney. LPS, a potent inducer of TNF- $\alpha$  secretion from DCs via the pattern recognition receptor (PRR) Toll-like receptor 4 (TLR4), can cause apoptosis of renal epithelium and acute renal failure (ARF). However, LPS can also engage TLR4 on other renal cell types, including renal epithelium.<sup>6</sup> The question has been, then, which specific TLR4<sup>+</sup> renal cells might mediate LPS-induced ARF and how it occurs. This was recently addressed by Cunningham and colleagues, who studied the renal response to LPS after cross-transplantation of kidneys between normal mice and TNFR-1-null mice,<sup>7</sup> or between normal mice and mice with inactive TLR4.<sup>8</sup> They discovered that TNFR-1-null kidneys placed in normal mice were protected from ARF caused by LPS, whereas normal kidneys placed in TNFR-1-null mice readily developed ARF.<sup>7</sup> In contrast, kidneys with inactive TLR4 developed LPS-induced ARF when placed in normal

mice, whereas normal kidneys placed in mice with inactive TLR4 developed mild ARF that eventually recovered.<sup>8</sup> Together, these studies suggest that LPS does not directly injure renal epithelium via TLR4 but activates other intra- and extrarenal TLR4<sup>+</sup> cell populations (for example, DCs) to produce TNF- $\alpha$  and damage renal epithelium via TNFR-1. Placing these studies on LPS-induced renal injury<sup>7,8</sup> in the context of those by Dong *et al.* on renal IRI,<sup>1</sup> one might reasonably question whether TNF- $\alpha$  is ever produced by renal cells other than renal DCs early after an insult at levels sufficient to cause autocrine- or paracrine-mediated injury via TNFR-1. Interestingly, TLR4 mediates IRI in the liver and in the heart.<sup>6</sup> If the same holds true in the kidney, then the study by Dong *et al.*<sup>1</sup> will be a primer for carefully exploring the TLR4<sup>+</sup> renal DC compartment before assigning mechanisms of injury to other TLR4<sup>+</sup> renal-cell compartments.

With resident renal DCs now identified as major inflammatory mediators in early renal IRI,<sup>1</sup> the possibility arises for direct targeting of renal DCs to help ameliorate renal IRI, particularly in allografts that could undergo pharmacologic preconditioning. For example, if resident renal DCs are stimulated to produce TNF- $\alpha$  by endogenous agonists of PRRs and not

by some other intrinsic mechanism during renal IRI, then defining the repertoire of responsible PRRs would allow for the selection of appropriate PRR antagonists to block or attenuate the activation of renal DCs.<sup>6</sup> Alternatively, signal transduction pathways downstream of PRRs could be targeted. One recent study demonstrated the potency of GSK-3 inhibition in modulating the downstream signaling from PRRs in DCs *in vivo*, where proinflammatory responses were switched into tolerogenic, anti-inflammatory responses (for example, secretion of interleukin-10) and mice were rendered completely resistant to the harmful effects of LPS.<sup>9</sup> This is intriguing because development of pharmacologic GSK-3 inhibitors is well under way for other renal diseases,<sup>10</sup> making them potentially attractive drugs for use in renal IRI as well. In summary, the surveying renal DC network is loudly sounding the alarm in renal IRI, and efforts to target the renal DC compartment in the kidney may help to combat this common form of renal injury.

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